


PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 101015-1 WO		FOR FURTHER ACTION		See Form PCT/PEA416	
International application No. PCT/GB2004/001614		International filing date (day/month/year) 14.04.2004		Priority date (day/month/year) 16.04.2003	
International Patent Classification (IPC) or national classification and IPC C07D403/12, A61K31/517, A61P35/00				CODE	DATE
				NTD	
Applicant ASTRAZENECA AB et al.				ANKOM	11 MAR 2005
<p>1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				DATA	
				ENTERED	
				FINAL	
4. This report contains indications relating to the following items:				CHECK	
<p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>					
Date of submission of the demand 29.10.2004			Date of completion of this report 09.03.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465			Authorized Officer Helps, I Telephone No. +49 89 2399-8209		

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10/552425

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-267 as originally filed

Claims, Numbers

1-25 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire International application,
- ☒ claims Nos. 23(part)
because:
 - ☐ the said International application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 23(part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-25
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-22,24,25
	No: Claims	23 see below

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this Written Opinion.

WO-A-02 00649	(A)
WO-A-01 21597	(B)
WO-A-95 15758	(C)
Cancer and Metastasis Reviews, vol.22, p.451-64 (2003)	(D)
Current Medicinal Chemistry, Anti Cancer Agents, vol. 3, p.23-34 (2003)	(E)
WO-A-2003 055491	(F)
WO-A-2004 058781	(G)
WO-A-2004 058752	(H)

The novel feature of the compounds of claim 1 is the 1-(arylaminoacarbonylmethyl)-pyrazol-4-yl group which is linked to the 4-position of the quinazoline ring via the group "X". The dependent claims 2-17, as well as claim 18 drawn to compounds of claim 1 for use as medicaments, claims 19-21 drawn to the use of compounds of claim 1 for the preparation of medicaments, claim 22 drawn to pharmaceutical compositions containing compounds of claim 1 and claims 24-25 drawn to processes for the preparation of compounds of claim 1 are novel by consequence.

Claims 1 to 25 therefore meet the Novelty requirements of Article 33(2) PCT.

Quinazolines bearing 4-heterocyclamino substituents at the 4-position have been described in the prior art documents (A)-(E), and been shown to have inhibiting action against Aurora kinase in documents (A) and (B). In document (A), which represents the closest prior art, 4-heterocyclamino quinazolines are described, in which the heterocyclic group is a five membered heteroaryl group such as thiazole, which bears a phenylaminocarbonylmethyl substituent (see table 1), or the heterocyclic group can represent other five membered rings such as imidazole or triazole. Starting from compounds in tables 1 and 2 of (A), compounds under the scope of the present application can be reached by replacing the arylaminocarbonylmethyl substituted thiazole group by a similarly substituted pyrazol-4-yl group. In document (B), further 4-heterocyclamino quinazolines are described in which the heterocyclic group is a six membered nitrogen containing heteroaryl, and in document (C), other 4-heterocycl

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substituted quinazolines as anti-proliferative agents are suggested.

Documents (D) and (E) are cited to give the background to the role of Aurora kinase in cancer development.

In view of the range of heterocyclic rings which may be present at the 4-position of the quinazoline ring as suggested by the prior art (pyrazole is suggested on page 7, line 4 of document (A)), the presently claimed compounds would have been considered by the skilled man as alternative Aurora kinase inhibitors to the exemplified compounds in the prior art . Consequently, the problem of providing further Aurora kinase inhibitors appears at first sight to have been solved in an obvious manner, and inventive step (Article 33(3) PCT) cannot be recognised.

Inventive step for the presently claimed compounds could be recognised if the Applicant could demonstrate an unexpected effect in comparison with the closest prior art as described above. The applicant is requested to submit all available information and argumentation in order to make credible the involvement of inventive step for the presently claimed compounds .

For the assessment of the present claim 23 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VIII CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

the term "prodrug thereof" used in claim 1 covers a non limiting range of derivatives of compounds of claim 1, and it has not been shown in any worked examples which derivatives (e.g. amides, carbamates, esters, etc.) actually have suitable pharmacokinetic properties which allow the parent compound to be administered in vivo. Thus "prodrugs" appear not to have been sufficiently disclosed.

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure

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(e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate documents (F), (G) and (H) may be taken into consideration for the evaluation of Novelty and/or inventive step.